ABSTRACT

Title of Document: **COMPARATIVE ANALYSIS OF THE EFFECTIVENESS AND SAFETY OF DRUG-ELUTING VERSUS BARE-METAL CORONARY STENTS AMONG PATIENTS REGISTERED IN THE MULTI-PAYER CLAIMS DATABASE.**

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The purpose of this study is to compare the safety and effectiveness of BMS versus DES in the coronary artery using unconventional and potentially more efficient post-market surveillance methods. A retrospective cohort study was conducted of 217,654 Medicare, Medicaid, and private insurance beneficiaries ages 41 years and older who were treated with coronary stenting between January 2007 and December 2010. Compared to BMS, DES use was associated with a significant reduction of myocardial infarction (Hazard Ratio (HR): 0.811; CI: [0.774, 0.84]), coronary artery bypass graft (HR 0.627; CI: [0.590, 0.666]), and repeat percutaneous coronary intervention (HR 0.910; CI: [0.888, 0.933]) at a median follow-up of 659 days. Use of DES was associated with superior CHD outcomes compared to BMS regardless of gender. Increased event-free probability for DES compared to BMS was seen among

whites and Asians for AMI, among whites only for CABG, and across all races for repeat stenting.

COMPARATIVE ANALYSIS OF THE EFFECTIVENESS AND SAFETY OF DRUG-ELUTING VERSUS BARE-METAL CORONARY STENTS AMONG PATIENTS REGISTERED IN THE MULTI-PAYER CLAIMS

By

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

List of Abbreviations

AMI	Acute myocardial infarction
BMS	bare-metal stent(s)
CCW	Chronic Conditions Warehouse
CHD	coronary heart disease
CMS	Centers for Medicare and Medicaid Services
CPT	Current Procedural Terminology
DAPT	Dual antiplatelet therapy
DES	drug-eluting stent(s)
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
HCPCS	Healthcare Common Procedure Coding System
ICD-9	International Classification of Diseases, 9th Revision
IRB	Institutional Review Board
MPCD	Multi-payer Claims Database
NHI	Normative Health Information
PCI	percutaneous coronary intervention
ST	Stent thrombosis
VLST	Very late stent thrombosis

I. INTRODUCTION

Coronary heart disease (CHD) caused approximately 1 out of every 7 deaths in the United States in 2011 and is expected to account for more than 23.6 million deaths per year by 2030 due to the obesity epidemic (Mozaffarian et al., 2015). Each year, 635,000 Americans experience a coronary attack for the first time, 300,000 have a recurrent attack, and an additional 155,000 experience silent first attacks (Mozaffarian et al., 2015). CHD is estimated to cost $320.1 billion per year in the U.S., with $195.6 billion in direct costs (i.e., hospital services, prescribed medications, home health care) and $124.5 billion in indirect costs (i.e., lost future productivity due to death). The annual cost of CHD is projected to rise to $1.13 trillion by 2030.

Coronary stents and balloon angioplasty, or percutaneous coronary intervention (PCI), are widely used procedures for patients with multi-vessel coronary artery disease. Stents are wire meshes placed in occluded arteries to prevent sudden closure of the artery. There are two main types of coronary stents: bare-metal and drug-eluting. A bare-metal stent (BMS) is a small, metal mesh tube that is permanently inserted to prevent the artery from closing up. Drug-eluting stents (DES) contain a polymer coating of antiproliferative agents that are intended to prevent the artery from closing in the long term. Shortly after the introduction of DES in April 2003, DES were used in 90% of lesions, but afterwards DES decreased to 64% of all stents according to the National Cardiovascular Data Registry (Krone et al., 2010). In the US, DES are now implanted in more than 500,000 patients annually (Stefanini & Holmes, 2013).

Between 2000 and 2010, the annual number of inpatient cardiovascular procedures (e.g., CABG, PCI) increased by 28% to 7,588,000 (Mozaffarian et al., 2015). The coronary stent market c is predicted to continue to increase in value from $4.89 billion in 2013 to $5.62 billion by 2020 (GlobalHealth, 2014). Given that DES cost about $1,846 more than BMS to manufacture and implant (Schafer et al., 2011) due to the unique biomaterial properties of DES, it is important to examine the cost effectiveness of these more expensive stent technologies.

In several studies, the implantation of DES resulted in lower rates of repeat revascularization, but did not show an advantage in mortality or recurrent myocardial infarction (MI) when compared to BMS (Laarman et al., 2006; Luca et al., 2009; Spaulding et al., 2006; Stone et al., 2009). Other CHD outcomes of interest include stent thrombosis (ST), the blockage of a stented vein or artery due to a clot, and very late stent thrombosis (VLST), the clotting of stented area over a year after the initial stent implantation procedure. Two studies found that VLST was more frequent among patients with DES (Brodie et al., 2011; Vink et al., 2011). In one of these studies, VLST was found almost exclusively after DES implantation (Brodie et al., 2011). DES patients who have experienced an AMI and have a history of ischemia have increased risk of ST or adverse side effects of antiplatelet agents (Fujimoto et al., 2008).

Reports from large registries and meta-analyses of randomized trials present inconclusive evidence of increased ST risk in DES (Douglas et al., 2009; Epstein, Ketcham, Rathore, & Groeneveld, 2012; Federspiel et al., 2012). ST after BMS typically occurs within the first 30 days after implantation, but VLST after DES can occur years afterward, with an annual incidence of 0.2% to 0.3% in patients with noncomplex

coronary artery disease and 0.4% to 0.6% after unrestricted use (Kirtane & Stone, 2011). More mechanistic, large-scale and long-term studies are therefore needed, especially by race and gender.

While randomized clinical trials may continue serving as the gold standard for comparing alternative treatments, observational studies offer a more cost-effective alternative to move research forward, particularly in light of recommendations to prioritize post market surveillance and detect long term effects of medical devices as early as possible. Among three previous observational studies that used administrative claims data, none found a decrease in unadjusted mortality risks for DES (Douglas et al., 2009; Federspiel et al., 2012; Malenka, Kaplan, Lucas, Sharp, & Skinner, 2008). Two of these studies found that DES led to a small decrease in ST-elevation myocardial infarction(Douglas et al., 2009; Malenka et al., 2008). Federspiel et al. (2012) examined DES and BMS effectiveness in 62,309 fee-for-service beneficiaries right around the time that DES were first introduced to the market (between 2003 and 2004), which may have influenced the types of patients who were receiving DES versus BMS.

Significant challenges remain in understanding racial and gender differences in cardiovascular risk factors and inclusion of racial/ethnic minority groups in clinical trials of therapeutic interventions (Ferdinand, 2006). Racial and gender disparities have also been noted in the response to stent type; however, due to limited data on racial/ethnic minorities receiving PCI, there is no conclusive evidence (Berger, Sanborn, Sherman, & Brown, 2004; Collins et al., 2010; Marks, Mensah, Kennard, Detre, & Jr, 2000; Maynard, Wright, Every, & Ritchie, 2001; Pradhan et al., 2008; Slater et al., 2003).

This thesis examined safety and effectiveness of DES versus BMS coronary stents among a sample of healthcare beneficiaries enrolled in the Multi-Payer Claims Database (MPCD) for at least 6 months to capture a larger demographic than pervious surveillance studies. A subset of claims data for beneficiaries who underwent a stent implantation between January 2007 and December 2010 was included in this analysis.

The MPCD is a combination of OptumInsights's Normative Health Information (NHI) group coverage database and a 15% sample of Medicare and Medicaid claims. Other analyses have used similar national claims databases (e.g., Medicare inpatient fee-for-service claims files) to compare the effectiveness of DES and BMS. However, the mean age of patients who received BMS and DES in 2009 were 65 and 64.4 years, respectively (Auerbach, Maeda, & Steiner, 2012). The majority of these patients would not have been included in previous studies limited to Medicare patients at least 66 years of age (Douglas et al., 2009; Federspiel et al., 2012). The MPCD offers the opportunity to look at CHD outcomes in younger patients because of the inclusion of NHI claims. Use of this private and public health insurance database may therefore reveal a more efficient approach to conduct these important post-market surveillance studies.

II. Specific Aims

The specific aims of the proposed study are to:

1) Compare effectiveness of DES versus BMS stents in preventing CHD outcomes for patients in a nationwide sample.

2) Determine whether the association between CHD outcomes and stent type varies by race.

3) Determine whether the association between CHD outcomes and stent type varies by gender.

The null hypotheses are that no difference exists between the safety and effectiveness of BMS and DES, and by race or gender. Given how commonly these permanent implants are used, it is critical to understand the comparative effectiveness and safety of DES and BMS in order for physicians and patients to make informed health care decisions.

III. BACKGROUND

Drug-eluting and Bare-metal Coronary Stents

In acute ST-segment elevation myocardial infarction, stenting has been shown to be the optimal treatment compared with medical therapy or angioplasty alone (Luca et al., 2008). Originally, bare-metal stents (BMS) improved procedural safety and no longer required a standby surgeon for this complex treatment after implantation. However, BMS implantation may lead to neointimal hyperplasia, restenosis, and the need for repeat revascularization. Stent thrombosis (ST) is an injury response that involves vascular smooth muscle cell migration and proliferation and proteoglycan deposition; it is an uncommon but serious complication that almost always presents as death or a large non-fatal myocardial infarction (MI) (Stone et al., 2007). This injury response is mainly responsible for restenosis after BMS implantation. This prompted the development of DES, which were designed to release pharmacological agents to inhibit the response to injury. Drugs released from DES (i.e., Paxitol, Sirulimus) have biological effects such as activation of signal transduction pathways and inhibition of cell proliferation (Lüscher et al., 2007). Farb (2003) found that DES offered significantly lower percentage endothelialization. The introduction of DES reduced the rates of restenosis and target-vessel revascularization to below 10%, based on initial clinical trials (Morice et al., 2002; Moses et al., 2003). Most thrombosis events occur within the first 10 days after implantation and it is rare to observe ST after the first month (Farb et al., 2003; Joner et al., 2006).

Safety and Effectiveness of Drug-eluting Stents

Although BMS and DES have proven to be a safe and effective treatment, their use may result in ST. ST can block the free flow of blood through an artery and cause a heart attack or even death. Recent studies have presented conflicting results as to the risk of ST with certain DES. Randomized clinical trials have not demonstrated an increased event-free probability of DES over BMS (Moses et al., 2003; Stone et al., 2004). However, several observational analyses suggest a higher event-free probability among patients with DES (Douglas et al., 2009; Mauri et al., 2008; Ogita et al., 2009; Tu et al., 2007). In several analyses, patients who received DES experienced a 23-25% relative reduction in subsequent myocardial infarction (Douglas et al., 2009; Hannan et al., 2007; Malenka et al., 2008; Stettler et al., 2007). In contrast, Brodie et al. found that VLST and reinfarction (>1 year) were more frequent with DES(2011). Another follow-up study found VLST almost exclusively after the use of DES (Vink et al., 2011). In addition, no difference in the incidence of definite or probable ST was seen, although very late ST was almost exclusively seen after the use of DES. The exact pathogenesis of ST is not fully understood; it may involve factors such as procedure-related factors, patient-related factors, and lesion characteristics.

It is difficult to measure CHD outcomes due to the long period of follow-up and experimental procedure that is required to accurately detect the effects of ST. The CHD outcomes of interest in this thesis include: acute myocardial infarction (AMI), repeat percutaneous intervention, and coronary artery bypass graft (CABG). AMI is an acute coronary syndrome that can occur during the unstable periods of coronary atherosclerosis. Progression of atherosclerosis is triggered and enhanced by several factors, which when there is activated inflammation in the vascular wall. AMI may be

minor in chronic disease and clinically silent for years, but may also be catastrophic and lead to sudden death or severe vasculature damage. AMI can be the first sign of CHD or may occur repeatedly in patients with chronic disease (Thygesen, 2007).

Treatment adherence is an important factor in ST pathogenesis. The 2006 American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines recommends that "after the PCI procedure, in patients with neither aspirin resistance, allergy, nor increased risk of bleeding, aspirin 325 mg daily should be given for at least 1 month after bare-metal stent implantation, 3 months after sirolimus-eluting stent implantation, and 6 months after paclitaxel-eluting stent implantation, after which daily chronic aspirin use should be continued indefinitely at a dose of 75 to 162 mg. (Level of Evidence: B)" (ACH/AMA, 2009). DES are useful as an alternative to BMS to reduce the risk of restenosis in cases in which the risk of restenosis is increased and the patient is likely to be able to tolerate and comply with prolonged dual antiplatelet therapy (DAPT) (Levine, 2011). BMS should be used in patients with high bleeding risk or an inability to comply with 12 months of DAPT, whether for economic reasons or other reasons (ACCF, 2011). Due to limited data on women and racial/ethnic minorities receiving percutaneous coronary intervention (PCI), there is little conclusive evidence of the safety and effectiveness of DES stents among racial/ethnic minorities. Black race emerged as a strong predictor of definite VLST even after multivariable analysis and adjustment for median income and clopidogrel compliance (Collins et al., 2010), suggesting that race needs to be examined further. A recent follow-up study using the National Cardiovascular Registry found that Black and Hispanic patients undergoing PCI had worse long-term outcomes relative to white and Asian patients (Kumar et al., 2013).

However, previous studies have produced conflicting results for PCI outcomes in black and white patients (Berger et al., 2004; Collins et al., 2010; Marks et al., 2000; Maynard et al., 2001; Pradhan et al., 2008; Slater et al., 2003). It is possible that higher CHD outcomes may vary by race due to a higher prevalence of comorbidities in racial/ethnic minority groups (Khambatta, Seth, Rosman, & Share, 2011).

Women have a higher risk of bleeding and excess dosing of CHD treatment (Alexander et al., 2006). Adverse drug reactions tend to occur more often in women and are most likely caused by inherent sex-differences in pharmacodynamics, such as body mass index and reduced glomerular filtration rate (Anthony & Berg, 2002). Changes in circulating estrogen levels during the menstrual cycle, pregnancy, or hormone replacement therapy can also affect CHD.

The MPCD dataset offers an opportunity to examine a large, nationwide dataset of medical claims that includes racial/ethnic minorities and females who underwent stent implantation. This thesis examines racial and gender differences in the safety and effectiveness of DES and BMS and can inform methodological approaches to treatment outcomes for safety and efficiency by race and gender using diverse data sources. The MPCD was used to detect signals and evaluate post-market data for medical products related to racial/ethnic minority health and women's health that have not been used in the past, and complements previous trials.

IV. Research Design and Methods

Overall Study Design

This study compared health outcomes in a representative sample of healthcare beneficiaries who received a DES or BMS. The study design was a retrospective cohort study using a representative sample of Medicare, Medicaid, and private insurance beneficiaries who were older than 41 years of age and who received coronary stenting between January 2007 and December 2010. This retrospective cohort used a follow-up period of 2 to 4 years until the end of data collection in December 2010. Outcomes were measured using relevant International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and Current Procedural Terminology (CPT) codes in claims data from the Multi-Payer Claims Database (MPCD) (see Appendix A).

In order to fulfill Study Aim 1, descriptive statistics were used to establish baseline characteristics for both stent type groups. To fulfill Study Aims 2 and 3, a comparative analysis of DES versus BMS for groups was stratified by gender (male/female) and race (white/black/Hispanic/Asian). Figure 2 depicts the exposure and outcome variables involved in treatment for CHD that were assessed in this project.

Data Source and Validation

The MPCD is a nationwide sample of Centers for Medicare & Medicaid Services (CMS) Chronic Conditions Warehouse (CCW) data and Normative Health Information (NHI) private-payer data collected between January 1, 2007, and December 31, 2010. The CCW sample contains all claims from a 15% random sample of Medicare beneficiaries. These data were compared with data from the U.S. Census Bureau Profiles and were found to be representative of the U.S. population. The MPCD followed the race

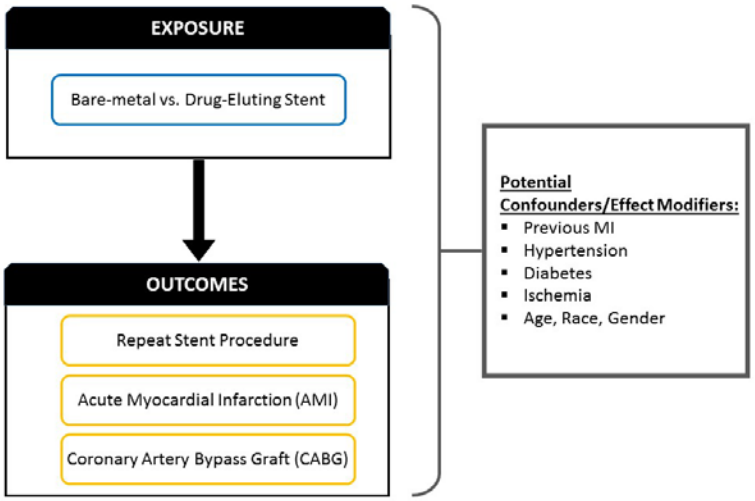

FIGURE 1. DIAGRAM DEPICTING EXPOSURE, OUTCOME, AND POTENTIAL CONFOUNDERS/EFFECT MODIFIERS THAT ARE INVOLVED IN TREATMENT FOR CHD.

and gender distribution of the total US population, with around 90% of the sample being represented by White, Black, and Hispanic races and were evenly split by male and female. As for age, the NHI subset of the data was the most representative of the US population, with 57.9% patients under 40 years of age, compared to 53.8% of the US population that is under 40 (OptumInsight, 2013). The analytic dataset includes a sample of coronary stent recipients among all payers within the NHI database, a geographically and demographically distributed sample of commercial claims. The vast majority of NHI data is group coverage. All of the outcome variables studied were categorical variables and were paired to the date of the event. This retrospective analysis is based on claim codes entered into the system by healthcare physicians, nurses and secretaries.

Description of the Participants and Criteria for Selection

A sample of 217,654 Medicare, Medicaid, and private health insurance beneficiaries continuously enrolled for six months, at least 41 years of age, who received a primary diagnosis of non-chronic coronary artery disease in a native vessel (ICD-9 code 414) and

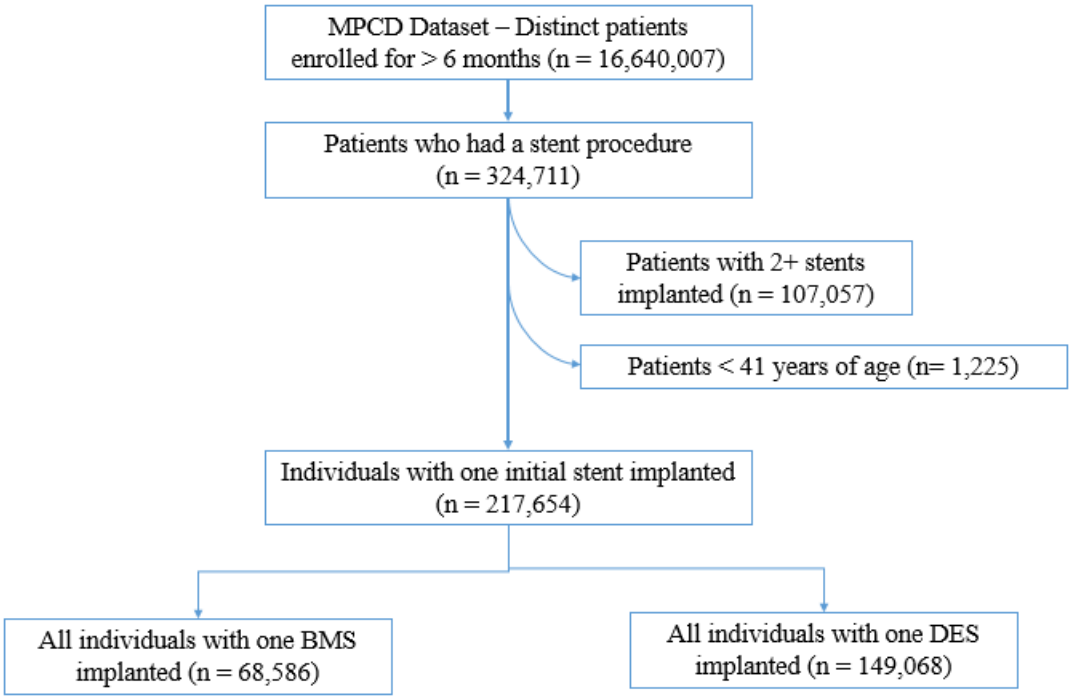

FIGURE 2. SCHEMATIC OF EXCLUSION AND INCLUSION CRITERIA FOR INDIVIDUALS IN THE MPCD.

underwent a stent implantation between January 2007 and December 2008 was identified from the MPCD database. Patients who underwent both DES implantation and BMS implantation procedures were excluded, as seen in Figure 2.

Main Exposure Variable: Stent Type

The exposure variable for this study is stent type, either BMS or DES. Patients who received a coronary stent were identified using ICD-9 procedure codes and

Healthcare Common Procedure Coding System codes. The type of stent implanted for each patient was identified as having received either BMS (36.06, C1876, C1877, 92980, 92981) or DES (36.07, C1874, C1875, G0290, G0291) using ICD-9 and HCPCS codes and matched to each individual by patient identifier number. The initial stent implantation was noted by the date associated with the initial stent procedure claim code. Consecutive procedures occurring within 7 days of one another were considered part of the same clinical episode. Duplicates were removed if multiple procedures were included in the procedures file for a single patient identifier number. Of these patients, 68,586 received at least one bare-metal stent and 149,068 received at least one DES stent between July 2007 and December 2008. Univariate analyses were conducted to compare BMS and DES patients using t-tests and chi-square tests in SAS 9.3. A significance level of 0.05 was used for all analyses.

Confounders

Information on coronary artery disease risk factors was collected from diagnosis files of patients included in MPCD dataset. Demographic information (i.e., age, gender, race) was collected from demographic files of patients in the MPCD and matched to each individual using a unique patient identifier number. Confounders were included in the Cox proportional hazards model if they altered the coefficient of the main variable by more than 10 percent. Effect modification was assessed by testing for interaction terms. Age was stratified into five year increments. Race was stratified into five categories: "White", "Black", "Hispanic", "Asian", "Other". Only one race could be selected per patient in the MPCD; therefore, there may be under-reporting of Hispanics. Variables that were associated to the CHD outcomes and were of interest to this study included

hypertension, ischemia, high cholesterol, and previous AMI. These binary variables were identified by matching the associated ICD-9 code with the unique patient identifier number.

Time-to-CHD Event Variables

For study aims 1-3, beneficiaries were followed for 2 to 4 years through December 2010. The incidence of CHD events among beneficiaries with a coronary stent implanted was examined by stent-type, and stratified by race (aim 2) or gender (aim 3). CHD events included death, AMI, PCI, and CABG. AMI (410.X1), CABG (36.10-36.19), and repeat or PCI (36.00, 36.06, 36.07, 36.09) were identified by ICD-9 CM diagnosis codes. Time-to-event variables were paired to each patient by calculating the time between. A censoring variable was also included to censor out any patients that were free of the event during the duration of the study. Surgeons use CABG, a type of surgery that improves blood flow to the heart to treat people who have severe CHD. During CABG, a healthy artery or vein from the body is connected to the blocked coronary artery to allow oxygen-rich blood to flow to the heart muscle. PCI consists of angioplasty and stenting. Angioplasty is a procedure to open narrowed or blocked coronary arteries and is typically followed by the implantation of a stent. Within the MPCD, the first angioplasty or stenting after the initial stent procedure was included as a CHD outcome. Data were right-censored for patients who continued to be enrolled in the MPCD throughout the duration of the study (December 2010) and never experienced a CHD outcome.

Data analysis

Study Aim 1: Baseline characteristics were compared between the group receiving DES versus BMS stents using a χ^2 test for categorical variables and a *t* test for continuous variables. The normality distribution was tested using the univariate analysis in SAS and looking at the normal probability plot (see Appendix C). This information was used to determine whether there was a significant difference in age, race, gender, and diagnoses distributions between patients receiving DES and patients receiving BMS. This was crucial to determining whether the baseline characteristics of both stent groups are comparable and which covariates needed to be adjusted for in the Cox proportional hazards model. Among the beneficiaries who received a stent procedure, a Kaplan Meier analysis at 2-year follow-up was used to estimate the CHD event-free probability (repeat PCI, CABG, AMI) by stent type (BMS and DES).

Study Aims 2 and 3: Among the beneficiaries who received a stent procedure, a Kaplan Meier analysis at 2-year follow-up was used to estimate the probability of CHD events (repeat PCI, CABG, AMI) by stent type, stratified by gender (female and male) or race (white/Black/Asian/Hispanic/other). Potential confounders included patient demographic variables (e.g., race, gender) and comorbidities (e.g., ischemia, high cholesterol, hypertension, previous AMI).

A Cox proportional hazards model was used to conduct a multivariate model adjustment. Significant covariates to include in the model were chosen by identifying the variables that produced a greater than 10% deviation from unadjusted hazard ratio. The model included covariates such as demographic variables (i.e., gender and race) as well as those comorbidities that were significantly different between stent type groups as seen in Table 1 (i.e., ischemia, high cholesterol, hypertension, previous AMI). In the

multivariate cox proportional hazards model, proportionality was tested for all covariates (See Appendix C). Analyses were also stratified by age group because the proportionality assumption did not hold for age, especially ages below 41.

Human Subjects Research

The MPCD was compiled using data from the NHI, Medicare, and Medicaid with funding from the American Recovery and Reinvestment Act. The Assistant Secretary for Planning and Evaluation worked with the Centers for Medicare and Medicaid Services to manage the generation of the MPCD and contract the work to OptumInsight. When compiling the MPCD, OptumInsight kept patient identifier numbers anonymous and grouped individuals into 5 year age cohorts for ease of reporting and to meet HIPAA privacy regulations. This study was deemed Health Insurance Portability and Accountability Act (HIPAA)-compliant and exempt from Institutional Review Board (IRB) review at the University of Maryland due to the anonymity of the patient identifiers in this dataset (see Appendix B).

V. RESULTS

Study Sample

Of the patients included in this sample, 63.4% were male, 39.9% had been diagnosed with diabetes, 52.8% with high cholesterol, 94.7% with ischemia, and 59.9% with hypertension. Patients receiving DES were slightly younger (average age of 71.2 years); were 63.9% male; and had a significantly higher percentage of Hispanics or Asians compared to patients receiving BMS (Table 1). Compared to patients who received BMS, patients who received DES were significantly more likely to have high

cholesterol, a history of myocardial infarction, or ischemia; and less likely to have hypertension. Of note is that observed differences in baseline demographic statistics by stent type are very small but statistically significant due to the large sample size. In the SAS univariate procedure, P-P, and Q-Q plots (see Appendix C), the data points do not seriously deviate from the fitted line, indicating that the continuous variable, age, is normally distributed.

TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF MPCD STENT PATIENT SAMPLE.

Demographic Characteristics	**BMS (n = 68,586)**		**DES (n = 149,068)**		***p***
Mean Age in Years ± SD	73.4 ± 9.9		71.2 ± 10.3		< 0.0001
Age Range	41-85 years		41-85 years		
Male	47,789	62.1%	112,769	63.9%	< 0.0001
Race					
White	58,842	85.8%	127,457	85.5%	< 0.0001
Asian	820	1.2%	2,633	1.8%	
Black	6,254	9.1%	12,248	8.2%	
Hispanic	1,810	2.6%	4,859	3.3%	
Other	860	1.3%	1,871	1.3%	

TABLE 2. COMORBIDITIES IN STENT PATIENT SAMPLE.

Health Characteristics	**BMS (n = 68,586)**		**DES (n = 149,068)**		***p***
	n	%	n	%	
Diabetes	31,013	40.3%	70,078	39.7%	0.0114
High Cholesterol	39,432	51.2%	94,362	53.5%	< 0.0001
Hypertension	48,262	62.7%	103,540	58.7%	< 0.0001
Ischemia	71,526	92.9%	168,466	95.5%	< 0.0001
Prior AMI	51,886	67.4%	128,777	73.0%	< 0.0001
Prior AMI - Within 30 Days of Stent	480	0.6%	1,011	0.6%	0.1229
Prior CABG	1,244	1.6%	2,727	1.6%	0.1978

Of the 142,816 who completed at least a 1-year follow-up, a total of 22,327 (15.8%) patients underwent a follow-up PCI; 3,372 (2.4%) underwent CABG; and 6,028 (4.2%) suffered from an AMI.

Overall, the event-free probability of repeat stent implantation, follow-up CABG, and AMI was higher among DES recipients than BMS recipients. Unadjusted Kaplan-Meier event curves depicted below show an increased CHD event-free probability for

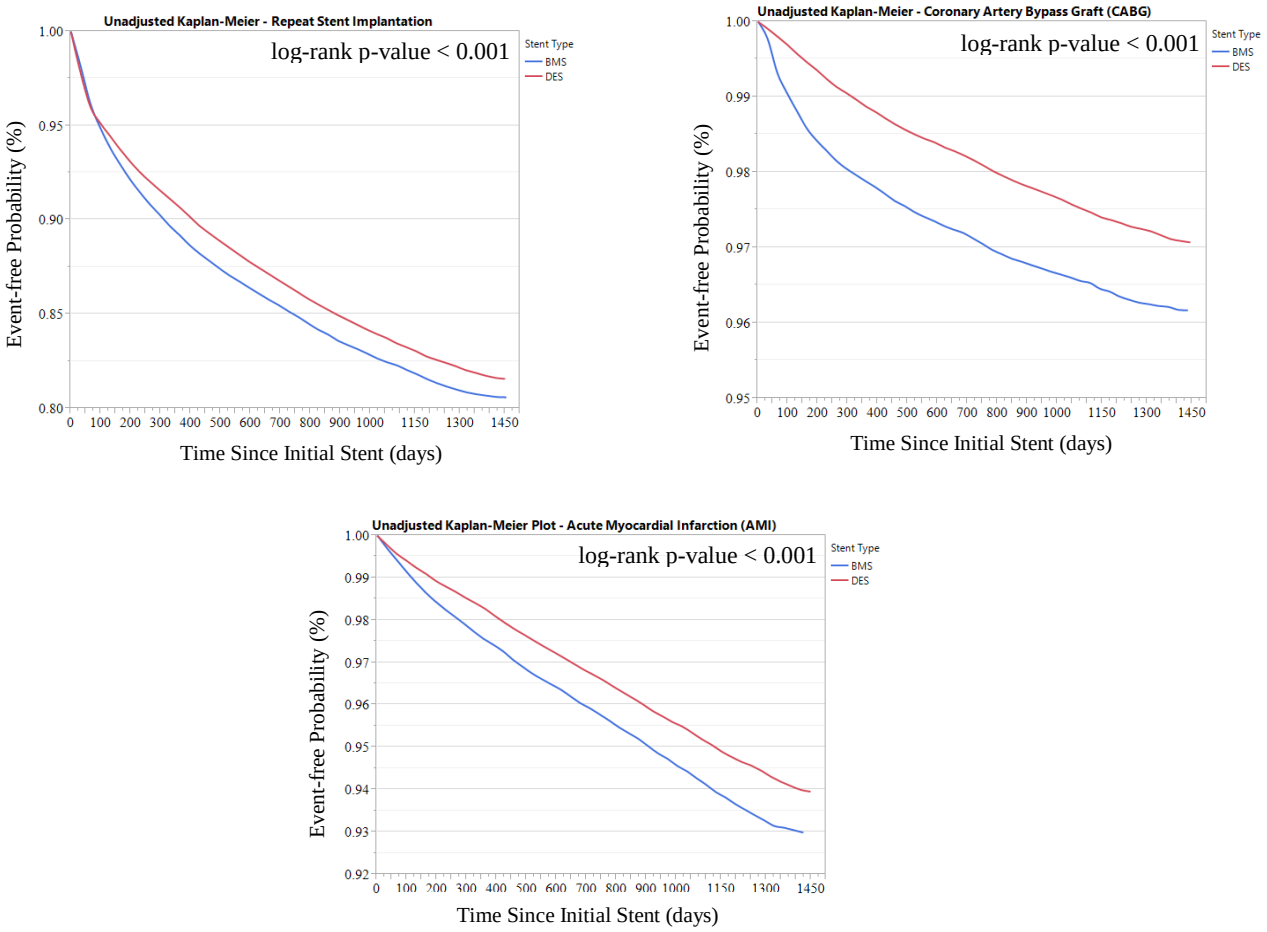

FIGURE 4. UNADJUSTED KAPLAN-MEIER PLOTS FOR HEALTH OUTCOMES.

DES as compared to BMS for each CHD event of interest (Figure 3). DES was associated with a significant cumulative hazard reduction in repeat PCI, AMI, and CABG.

As seen in Table 3, females were at increased hazard of AMI and decreased hazard of CABG compared to males. Compared to Whites, Black patients were at

increased hazard of AMI and Asian patients were at decreased hazard of AMI. No significant interaction was found between stent type and gender or race.

TABLE 3. COVARIATE-ADJUSTED HAZARDS RATIOS [95% CONFIDENCE INTERVALS].[1]

	AMI	**CABG**	**Repeat PCI**	Interaction Term
Unadjusted	0.799 (0.764 , 0.835)	0.643 (0.606 , 0.683)	0.918 (0.896 , 0.940)	
Adjusted	0.808 (0.772 , 0.847)	0.627 (0.590 , 0.666)	0.909 (0.887 , 0.931)	
Gender (Ref = Male)				0.7190 (P =0.3965)
Female	**1.053 (1.006, 1.103)**	**0.823 (0.873 , 0.876)**	0.997 (0.973 , 1.021)	
Race (Ref = White)				6.5156 (P =0.1638)
Black	**1.325 (1.234, 1.423)**	0.960 (0.860 , 1.071)	**1.079 (1.036, 1.123)**	
Hispanic	1.044 (0.918, 1.187)	0.899 (0. 749, 1.079)	**0.896 (0.835, 0.962)**	
Asian	**0.809 (0.644, 0.987)**	0.835 (0.644 , 1.083)	0.965 (0.879 , 1.060)	
Other	1.233 (1.023, 1.487)	1.149 (0.894, 1.476)	**1.079 (1.132 , 1.370)**	

The Cox proportional hazards model was stratified by gender and race to fulfill aims 2 and 3. A decreased hazard of CABG was seen across all races and both genders, but a benefit of DES was seen only across Whites in AMI and repeat PCI and only across Asians in AMI. The stratified analysis in Table 4 suggests that gender and race are effect modifiers, and they were not included in the final Cox proportional hazards model.

[1] Cox Proportional Hazards for DES compared to BMS. Adjusted for comorbidities: ischemia, high blood pressure, high cholesterol, and previous AMI.

TABLE 4. COVARIATE-ADJUSTED HAZARD RATIOS, STRATIFIED BY GENDER AND RACE.[2]

	AMI	CABG	Repeat PCI
Unadjusted	0.799 (0.764 , 0.835)	0.643 (0.606 , 0.683)	0.918 (0.896 , 0.940)
Adjusted	0.808 (0.772 , 0.847)	0.627 (0.590 , 0.666)	0.909 (0.887 , 0.931)
By Gender			
Male	**0.791 (0.748 , 0.838)**	**0.601 (0.561 , 0.644)**	**0.908 (0.881 , 0.935)**
Female	**0.816 (0.761 , 0.876)**	**0.677 (0.613 , 0.747)**	**0.893 (0.860 , 0.928)**
By Race			
White	**0.806 (0.766 , 0.848)**	**0.623 (0.584 , 0.664)**	**0.909 (0.886 , 0.934)**
Black	0.874 (0.761 , 1.002)	**0.797 (0.643 , 0.988)**	0.927 (0.856 , 1.005)
Hispanic	0.828 (0.629 , 1.090)	**0.510 (0.354 , 0.736)**	0.865 (0.742 , 1.009)
Asian	**0.502 (0.333 , 0.755)**	**0.480 (0.282 , 0.818)**	0.830 (0.672 , 1.025)
Other	0.876 (0.592 , 1.296)	**0.469 (0.285 , 0.773)**	0.996 (0.811 , 1.222)

Once adjusted for race and gender, the Cox proportional hazards model produced estimates showing association between stent type and all CHD outcomes. Results were stratified by age because not all age groups passed the test of proportionality, specifically those patients under the age of 41 (see Appendix D). The hazard ratio for DES compared with BMS was 0.811 (95% confidence interval [CI]: [0.774 , 0.849]) for AMI, 0.627 (CI: [0.590, 0.666]) for CABG, and 0.910 (CI: [0.888, 0.933]) for a repeat PCI (Table 5). There was a significant event-free benefit of DES over BMS in those 66 and over for AMI; in those 46 and over for CABG; and those 61 and over for repeat PCI.

[2] Cox Proportional Hazards for DES compared to BMS. Adjusted for comorbidities: ischemia, high blood pressure, high cholesterol, and previous AMI and stratified by gender and race.

TABLE 5. COVARIATE-ADJUSTED HAZARDS RATIOS [95% CONFIDENCE INTERVALS], STRATIFIED BY AGE.[3]

	AMI	CABG	Repeat PCI
Unadjusted	0.799 (0.764 , 0.835)	0.643 (0.606 , 0.683)	0.918 (0.896 , 0.940)
Adjusted	0.811 (0.774 , 0.849)	0.627 (0.590 , 0.666)	0.910 (0.888 , 0.933)
By Age Group			
41-45	0.825 (0.484 , 1.406)	0.686 (0.354 , 1.331)	0.863 (0.638 , 1.168)
46-50	1.218 (0.833 , 1.781)	**0.541 (0.375 , 0.778)**	1.058 (0.876 , 1.278)
51-55	0.914 (0.711 , 1.174)	**0.569 (0.432 , 0.751)**	0.915 (0.800 , 1.047)
56-60	0.867 (0.703 , 1.068)	**0.610 (0.484 , 0.768)**	0.911 (0.817 , 1.017)
61-65	0.957 (0.803 , 1.142)	**0.510 (0.418 , 0.623)**	**0.841 (0.767 , 0.921)**
66-70	**0.633 (0.554 , 0.723)**	**0.588 (0.502 , 0.688)**	**0.815 (0.762 , 0.871)**
71-75	**0.768 (0.692 , 0.854)**	**0.571 (0.502 , 0.648)**	**0.899 (0.852 , 0.948)**
76-80	**0.758 (0.679 , 0.845)**	**0.584 (0.509 , 0.670)**	**0.908 (0.858 , 0.961)**
81-85	**0.879 (0.809 , 0.954)**	**0.703 (0.615 , 0.805)**	**0.946 (0.903 , 0.990)**

[3] Cox Proportional Hazards for DES compared to BMS. Adjusted for comorbidities: ischemia, high blood pressure, high cholesterol, and previous AMI and stratified by age.

VI. DISCUSSION

In this retrospective study of health insurance beneficiaries receiving a stent, we compared results using a Cox proportional hazards modeling approach to account for confounding effects of covariates. The findings from this study of beneficiaries are consistent with other observational studies that found improved CHD outcomes (i.e., decreased rates of repeat PCI, CABG, and AMI) for patients with DES as compared to BMS (Federspiel et al., 2012; Malenka et al., 2008). However, since mortality data were missing in the MPCD database and death could not be analyzed as a CHD outcome, no comparisons could be made with results from other studies regarding event-free probability.

Observed differences in baseline demographic statistics by stent type are very small but may be statistically significant due to the large sample size.

Stratifying by race revealed an increased event-free probability of DES over BMS in looking at AMI as a health outcome only among Whites and Asians. In future studies, it would be interesting to look into why there is no clear benefit of DES over BMS in Blacks and Hispanics. This study did not take into account DAPT adherence or a socio-economic variable (e.g., zip code, health insurance type) but further analysis into these variables in the MPCD may provide additional information. As for gender, a significantly lower hazard of AMI, CABG, and repeat PCI was seen for both genders.

One limitation of using administrative claims data is that residual confounding may exist due to lack of detail on the type and number of stents implanted (e.g., not enough information to distinguish multiple stents in one procedure versus multiple procedures) and inaccurate insurance claim codes (e.g., confusion with HCPCS and ICD-9 when a patient switches between the NHI and Medicare). Since the data are

observational and dependent on healthcare staff responsible or entering the data, the way an insurance claim is interpreted and entered into the system could lead to varying levels of accuracy and completeness from healthcare center to healthcare center. The MPCD dataset was validated against data from the US Census Bureau to account for underreporting or misclassification of events (OptumInsight, 2013). Previous studies using a similar claims database lacked detailed information about patient clinical characteristics and emphasized the importance of adjusting for baseline characteristics (Douglas et al., 2009; Epstein, Polsky, Yang, Yang, & Groeneveld, 2011).

A major limitation is that mortality records were incomplete and survival rates could not be calculated for DES versus BMS. Because this was a retrospective study, I was unable to request additional information on variables of interest and analyze in more detail. For example, details on where the stent was placed in the vasculature and how the stent was implanted were incomplete. With more detailed insurance claim codes, it would be possible to decipher between single stent and multi-stent procedures. Also, the type of drug being eluted by DES is not specified in the MPCD. As technology improves and DES become more diverse (i.e., Paxitol-eluting, Sirulimus-eluting), significant differences in CHD outcomes may result from these different types of stents.

Future studies should include cost effectiveness studies to address the increased cost of DES due to additional manufacturing costs to coat the stent with the drug polymer and research and development. They should also consider implementing a data collection method that allows for proper matching to death records, especially since the CHD outcomes of interest in this study could not cover all other possible outcomes (i.e., VLST, restenosis, target-vessel revascularization). Other potential confounders that should be

examined include zip code and other proxies for socioeconomic status that may indicate that access to care is an important factor to successful outcomes from stent implantation. Since the MPCD contains a code for the type of health insurance, it would be interesting to explore health insurance type and examine differences in health outcomes between commercial and public health insurance carriers. Furthermore, since adherence to DAPT is so critical to ensure positive health outcomes after DES implantation, it would be beneficial to analyze drug adherence rates. This may explain observed differences between races as well as by age. For example, older patients may have a more difficult time remembering to take their daily medications.

Other analytic approaches could be considered by future studies, such as propensity score matching, to estimate the effect of BMS and DES while accounting for covariates. Propensity score matching may also take into account covariates that reduce the potential for bias in treatment (BMS vs. DES) selection since stent guidance is at the discretion of the treating physician. It would be interesting to see if insurance type (i.e., private versus public) affects the decision to implant BMS and DES. Once a few additional statistical methods are explored, it would be beneficial to compare these measures to clinical outcomes from other study types to evaluate and validate the potential surveillance utility of this dataset.

Conducting an observational analysis using claims data provides a better understanding of BMS versus DES utilization across beneficiaries at the population level at a significantly lower cost and greater generalizability than randomized clinical trials. The MPCD dataset that was used in this analysis is readily available, providing the advantage of efficiency related to cost and time. Given that the results from this MPCD

study provided similar results to existing studies, the MPCD may be valid for quick adverse effect surveillance. With quicker surveillance, negative health outcomes could be detected faster than current methods and health complications nationwide could be avoided. In order to validate the MPCD as a tool for detecting adverse effects, these surveillance studies should look on the same outcome (i.e., AMI, repeat stent) and the same study period (January 2007 to December 2010).

V. Public Health Significance

More than 15 million, or six percent, of Americans have been diagnosed with CHD (Mozaffarian et al., 2015). Coronary atherosclerosis is responsible for more than 9 million ambulatory care visits and more than 700,000 hospitalizations. Among adults younger than 65 years, Medicaid beneficiaries were more likely to be diagnosed with any type of heart disease, compared to those with private insurance or uninsured (Pleis, Ward, & Lucas, 2009). It is estimated that 22 per 10,000 adults receive a stent, with even higher rates for the elderly (73 per 10,000 among 65 and older) (Kochanek, Xu, Murphy, Minino, & Kung, 2012).

Given how common coronary stents are, it is important to understand the comparative effectiveness and safety of these devices. This information will be useful for physicians and patients to make informed health care decisions. This study addresses the need for evaluation of comparative performance (effectiveness and safety) between BMS and DES that are already on the market among a nationwide sample. Previous nationwide comparisons between these two types of stents have only included Medicare beneficiaries or only included managed care beneficiaries (Douglas et al., 2009; Federspiel et al., 2012; Meadows et al., 2012), whereas the MPCD includes private insurance claims among younger patients. The use of claims data enables low-cost, observational analyses that evaluate real-world usage patterns and populations on a regular basis at a reasonable cost.

This dataset could be applied to improving post-market surveillance of medical devices. In the case of BMS versus DES, this dataset produced comparable results to other retrospective studies on Medicare claims. With the coverage of Medicare, Medicaid and private payer beneficiaries and follow-up time of up to 3.5 years, it has the potential

to provide insight into long-term adverse effects that haven't been explored previously; in the case of stents, onset of ST and VLST were explored. In order to incorporate regular use of this database for monitoring of adverse events, studies on health outcomes could be explored for other medical devices of interest. Once it is established that statistical measures obtained from the MPCD are reliable, measures could be taken to shorten the turnaround time between data collection and analysis so that adverse effects can be detected within a few weeks. This would be useful for monitoring adverse effects of new medical devices when they are introduced to the market. Conditions that are clearly identified in insurance databases by HCPCS and ICD-9 codes would lend themselves well to use of this type of surveillance. There would have to be an emphasis on maintaining complete records of patients (e.g., ensuring that all comorbidities are included in the patient record). This database would require additional resources to continuously update, maintain, and monitor. While there would be an increase in cost to more rapidly compile this insurance claim data, the MPCD would offer a long-term benefit of being able to collect these measures and take a device off the market in time to prevent additional adverse effects in patients.

VI. MPH Competencies Addressed in Thesis

I addressed the following MPH competencies throughout my thesis: 1-14. Figure 3 illustrates the complete list of the competencies for a MPH in Epidemiology and those that were addressed through my internship and thesis.

Table 6. Competencies for MPH in Epidemiology Internship/Thesis

Competencies for MPH in Epidemiology Internship/Thesis	**Internship**	**Thesis**
1. Demonstrate the importance of epidemiology for informing scientific, ethical, economic, and political discussion of health issues.	**X**	**X**
2. Assess a public health problem in terms of magnitude, person, time and place.	**X**	**X**
3. Distinguish among the basic terminology and definitions of epidemiology.	**X**	**X**
4. Discriminate key sources of data for epidemiological purposes.	**X**	**X**
5. Calculate basic epidemiology measures.	**X**	**X**
6. Identify the principles and limitations of public health screening programs.	**X**	**X**
7. Evaluate the strengths and limitations of epidemiologic reports.	**X**	**X**
8. Draw appropriate inferences from epidemiologic data.	**X**	**X**
9. Explain criteria for causality.		**X**
10. Calculate advanced epidemiology measures.		**X**
11. Communicate epidemiologic information to lay and professional audiences.	**X**	**X**
12. Compare basic ethical and legal principles pertaining to the collection, maintenance, use and dissemination of epidemiologic data.	**X**	**X**
13. Design, analyze, and evaluate an epidemiologic study.	**X**	**X**
14. Design interventions to reduce prevalence of major public health problems.		**X**
15. Demonstrate program administration and organizational leadership.	**X**	

APPENDIX A. ICD-9 AND HCPCS CODES TO BE USED IN ANALYSIS [NCHS, 2010]

Stent Implantation

	PROCEDURE CODE	DESCRIPTION
ICD-9	0045	Insertion of one vascular stent
	0046	Insertion of two vascular stents
	0047	Insertion of three vascular stents
	0048	Insertion of four or more vascular stents
	0055	Insertion of drug-eluting stent(s) of other peripheral vessel(s)
	0060	Insertion of drug-eluting stent(s) of superficial femoral artery
	0063	Percutaneous insertion of carotid artery stent(s)
	0064	Percutaneous insertion of other extracranial artery stent(s)
	0065	Percutaneous insertion of intracranial vascular stent(s)
	0066	Percutaneous transluminal coronary angioplasty [PTCA]
	3606	Insertion of non-drug-eluting coronary artery stent(s)
	3607	Insertion of drug-eluting coronary artery stent(s)
CPT	92980	Transcatheter placement of an intracoronary stent(s), percutaneous,with or without other therapeutic intervention, any method; single vessel.
	92981	each additional vessel
	0075T	Transcatheter placement of extracranial vertebral or intrathoracic carotid artery stent(s), including radiologic supervision and interpretation, percutaneous; initial vessel.
	0076T	each additional vessel
	37205	Transcatheter placement of an intravascular stent(s) (except coronary, vertebral, iliac and lower extremity arteries), percutaneous; initial vessel
	37206	Transcatheter placement of an intravascular stent(s) (except coronary, vertebral, iliac and lower extremity arteries), percutaneous; each additional vessel (List separately in addition to code for primary procedure)
	37207	Transcatheter placement of an intravascular stent(s) (except coronary, vertebral, iliac and lower extremity arteries), open; initial vessel
	37208	Transcatheter placement of an intravascular stent(s) (except coronary, vertebral, iliac and lower extremity

		arteries), open; each additional vessel (List separately in addition to code for primary procedure)
	37215	Transcatheter placement of intravascular stent(s), cervical carotid artery, Percutaneous; with distal embolic protection
	37216	Transcatheter placement of intravascular stent(s), cervical carotid artery, percutaneous; without distal embolic protection
HCPCS	G0290	Transcatheter placement of a drug eluting intracoronary stent(s), percutaneous, with or without other therapeutic intervention, any method; single vessel
	G0291	Transcatheter placement of a drug eluting intracoronary stent(s), percutaneous, with or without other therapeutic intervention, any method; each additional vessel
	C1874	Stent, coated/covered, with delivery system
	C1875	Stent, coated/covered, without delivery system
	C1876	Stent, non-coated/non-covered, with delivery system
	C1877	Stent, non-coated/non-covered, without delivery system
ICD-9	3990	Insertion of non-drug-eluting peripheral (non-coronary) vessel stent(s)
	0040	Procedure on single vessel
	0041	Procedure on two vessels
	0042	Procedure on three vessels
	0043	Procedure on four or more vessels
	0044	Procedure on vessel/bifurcation

CHD Outcomes

Myocardial Infarction		
ICD_9 Codes	41000	Acute myocardial infarction of anterolateral wall, episode of care unspecified
	41001	Acute myocardial infarction of anterolateral wall, initial episode of care
	41002	Acute myocardial infarction of anterolateral wall, subsequent episode of care
	41010	Acute myocardial infarction of other anterior wall, episode of care unspecified
	41011	Acute myocardial infarction of other anterior wall, initial episode of care
	41012	Acute myocardial infarction of other anterior wall, subsequent episode of care
	41020	Acute myocardial infarction of inferolateral wall, episode of care unspecified
	41021	Acute myocardial infarction of inferolateral wall, initial episode of care
	41022	Acute myocardial infarction of inferolateral wall, subsequent episode of care

	41030	Acute myocardial infarction of inferoposterior wall, episode of care unspecified
	41031	Acute myocardial infarction of inferoposterior wall, initial episode of care
	41032	Acute myocardial infarction of inferoposterior wall, subsequent episode of care
	41040	Acute myocardial infarction of other inferior wall, episode of care unspecified
	41041	Acute myocardial infarction of other inferior wall, initial episode of care
	41042	Acute myocardial infarction of other inferior wall, subsequent episode of care
	41050	Acute myocardial infarction of other lateral wall, episode of care unspecified
	41051	Acute myocardial infarction of other lateral wall, initial episode of care
	41052	Acute myocardial infarction of other lateral wall, subsequent episode of care
	41060	True posterior wall infarction, episode of care unspecified
	41061	True posterior wall infarction, initial episode of care
	41062	True posterior wall infarction, subsequent episode of care
	41070	Subendocardial infarction, episode of care unspecified
	41071	Subendocardial infarction, initial episode of care
	41072	Subendocardial infarction, subsequent episode of care
	41080	Acute myocardial infarction of other specified sites, episode of care unspecified
	41081	Acute myocardial infarction of other specified sites, initial episode of care
	41082	Acute myocardial infarction of other specified sites, subsequent episode of care
	41090	Acute myocardial infarction of unspecified site, episode of care unspecified
	41091	Acute myocardial infarction of unspecified site, initial episode of care
	41092	Acute myocardial infarction of unspecified site, subsequent episode of care
HCPCS	G8006	Acute myocardial infarction: patient documented to have received aspirin at arrival
	G8007	Acute myocardial infarction: patient not documented to have received aspirin at arrival
	G8009	Acute myocardial infarction: patient documented to have received beta-blocker at arrival
	G8010	Acute myocardial infarction: patient not documented to have received beta-blocker at arrival
Repeat Percutaneous Coronary Intervention		
ICD_9	0045	Insertion of one vascular stent
	0046	Insertion of two vascular stents
	0047	Insertion of three vascular stents

	0048	Insertion of four or more vascular stents
	3606	Insertion of non-drug-eluting coronary artery stent(s)
	3607	Insertion of drug-eluting coronary artery stent(s)
CPT	92980	Transcatheter placement of an intracoronary stent(s), percutaneous,with or without other therapeutic intervention, any method; single vessel.
	92981	each additional vessel
HCPCS Codes	G0290	Transcatheter placement of a drug eluting intracoronary stent(s), percutaneous, with or without other therapeutic intervention, any method; single vessel
	G0291	Transcatheter placement of a drug eluting intracoronary stent(s), percutaneous, with or without other therapeutic intervention, any method; each additional vessel
	C1874	Stent, coated/covered, with delivery system
	C1875	Stent, coated/covered, without delivery system
	C1876	Stent, non-coated/non-covered, with delivery system
	C1877	Stent, non-coated/non-covered, without delivery system
Coronary Artery Bypass Graft		
ICD_9 Codes	36.1x	Aortocoronary bypass for heart revascularization, not otherwise specified
	3610	(Aorto)coronary bypass of one coronary artery
	3611	(Aorto)coronary bypass of two coronary arteries
	3612	(Aorto)coronary bypass of three coronary arteries
	3613	(Aorto)coronary bypass of four or more coronary arteries
	3614	Single internal mammary-coronary artery bypass
	3615	Double internal mammary-coronary artery bypass
	3616	Abdominal-coronary artery bypass
	3617	Other bypass anastomosis for heart revascularization
	3619	Heart revascularization by arterial implant
	362	Open chest transmyocardial revascularization
	3631	Other transmyocardial revascularization
	3632	Endoscopic transmyocardial revascularization
	3633	Percutaneous transmyocardial revascularization
	3634	Other heart revascularization
HCPCS	33510-33523	
	33530	
	33533-33536	

APPENDIX B. IRBNET BOARD DOCUMENT

FW: IRBNet Board Document Published

Olivia Denise Carter-Pokras <opokras@umd.edu> Mon, Jan 27, 2014 at 1:46 PM
To: Jessica G Bermudez <jess11@umd.edu>

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From: Joseph Smith [no-reply@irbnet.org]
Sent: Monday, January 27, 2014 1:40 PM
To: Olivia Denise Carter-Pokras
Subject: IRBNet Board Document Published

Please note that University of Maryland College Park (UMCP) IRB has published the following Board Document on IRBNet:

Project Title: [564930-1] Comparative Analysis of the Effectiveness and Safety of Drug-eluting Versus Bare-metal Coronary Stents Among Patients Registered in the Multi-Payer Claims Database
Principal Investigator: Carter-Pokras Olivia

Submission Type: New Project
Date Submitted: January 27, 2014

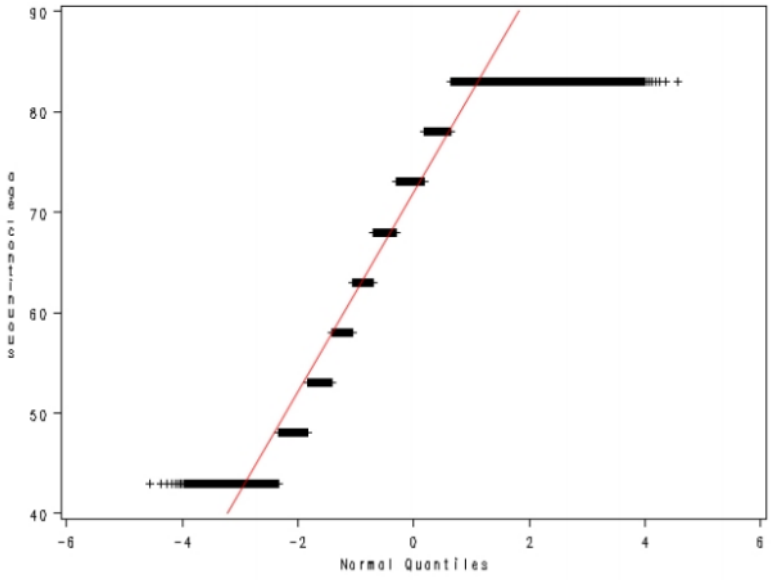
Document Type: Not Research Letter
Document Description: Not Research Letter
Publish Date: January 27, 2014

Should you have any questions you may contact Joseph Smith at jsmith54@umd.edu.

Thank you,
The IRBNet Support Team

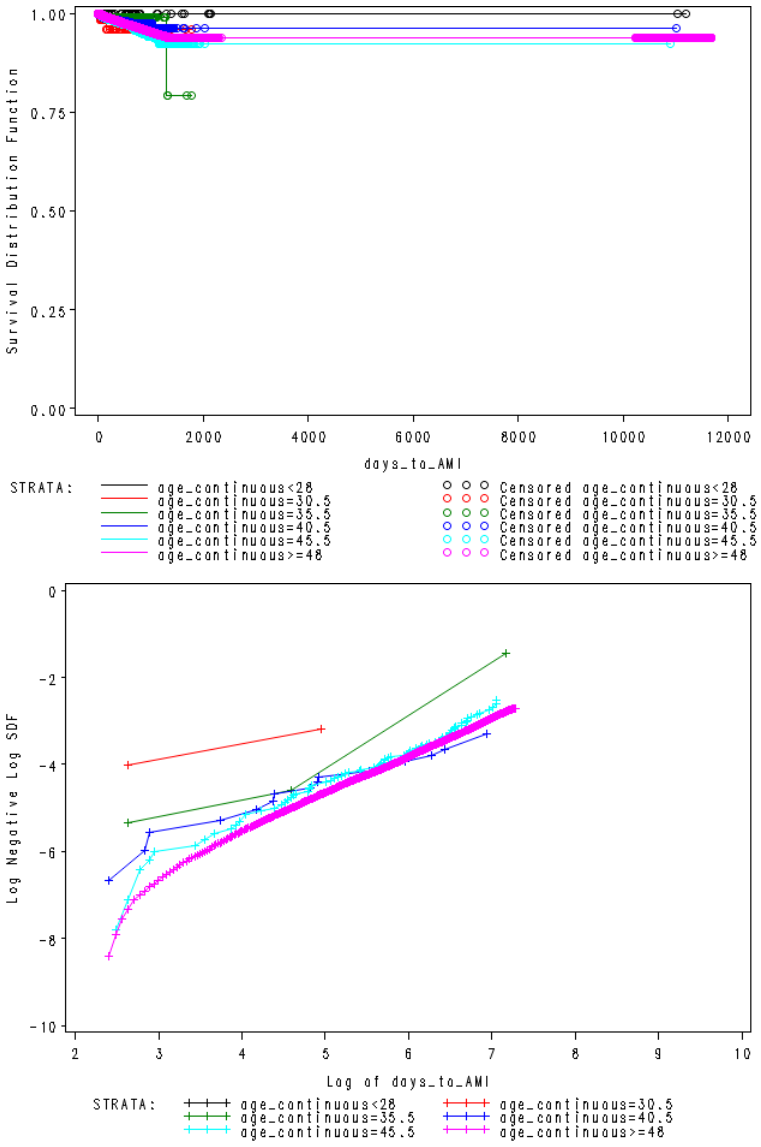
www.irbnet.org

APPENDIX C. TESTS OF NORMALITY

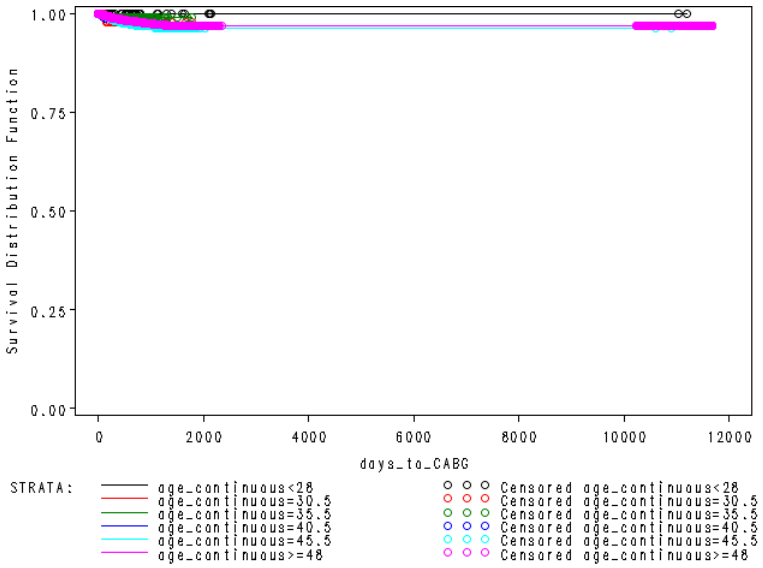


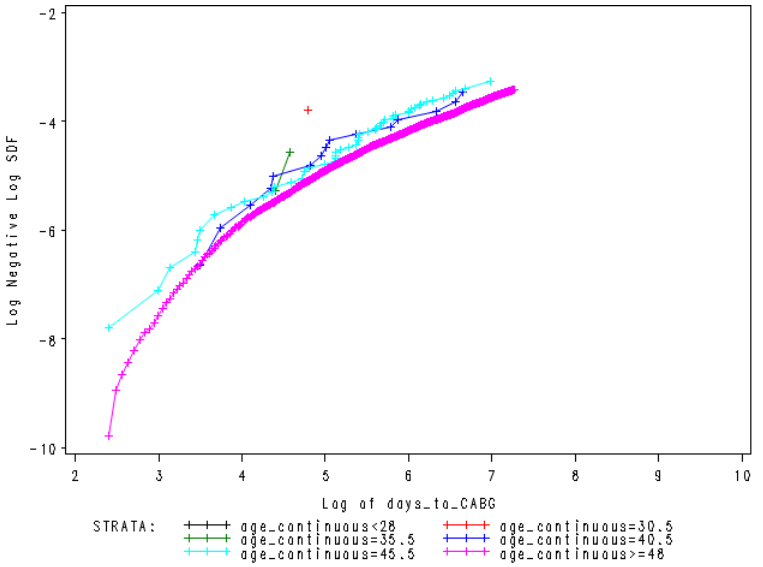
APPENDIX D. TESTS OF PROPORTIONALITY

Test of proportionality (CHD outcome = AMI) across lower age strata.

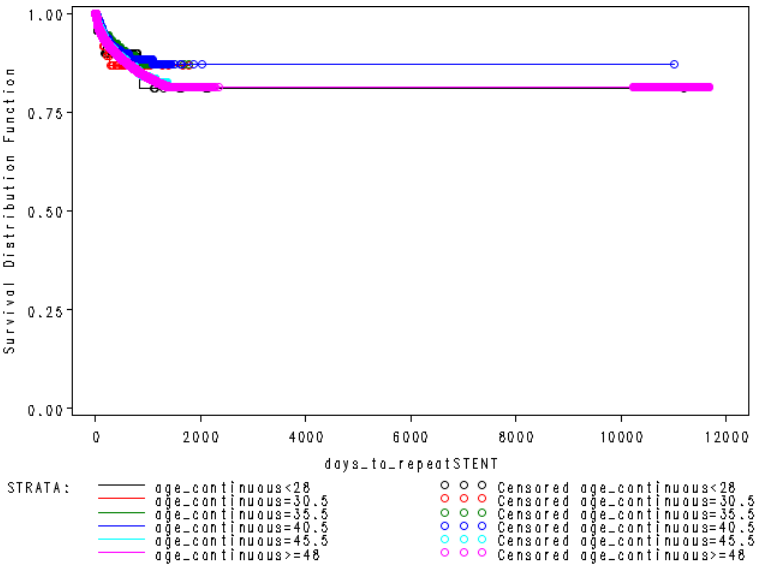


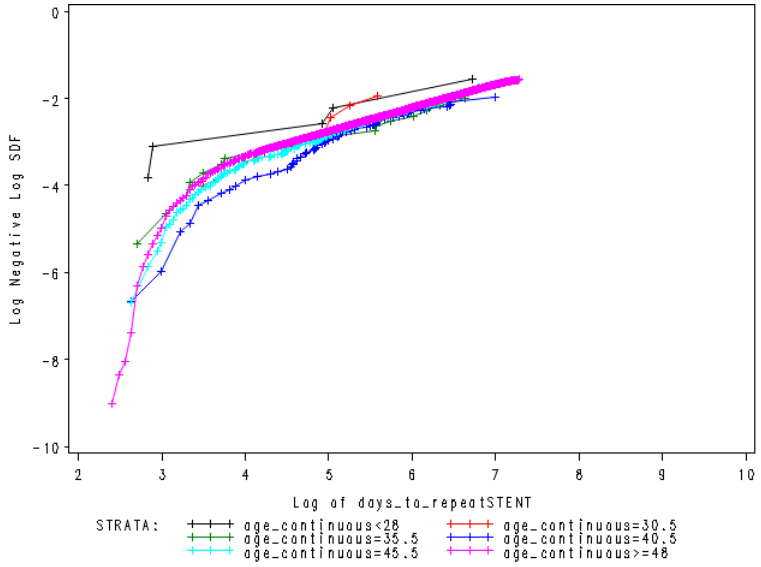
Test of proportionality (CHD outcome = CABG) across lower age strata.



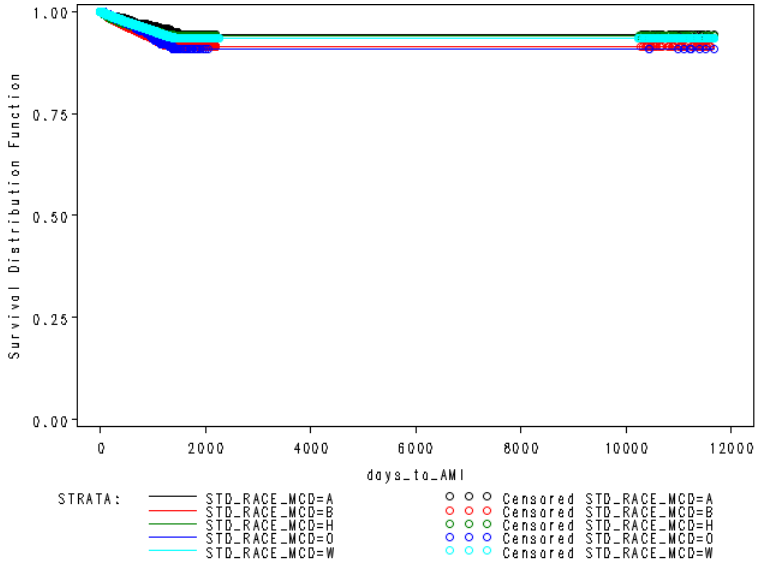


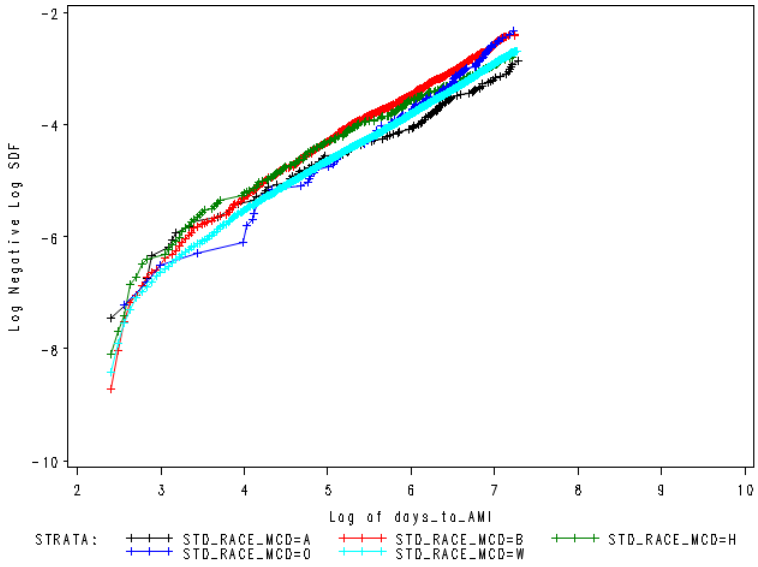
Test of proportionality (CHD outcome = repeat stent) across lower age strata.



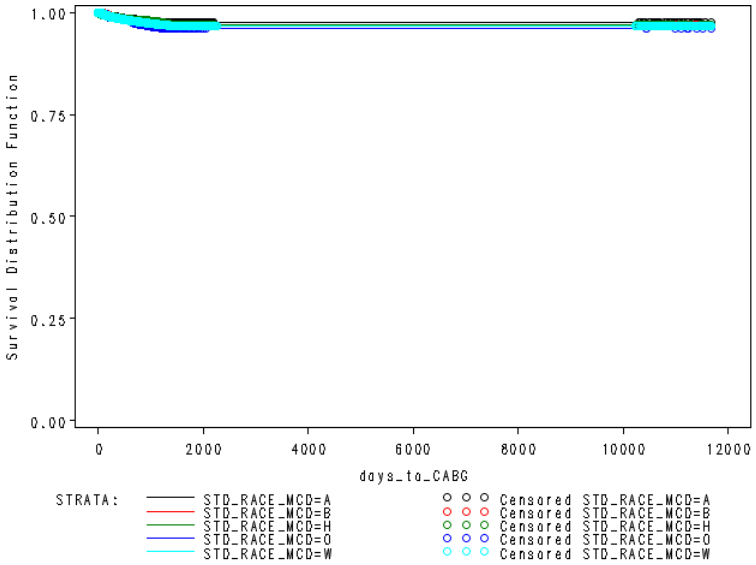


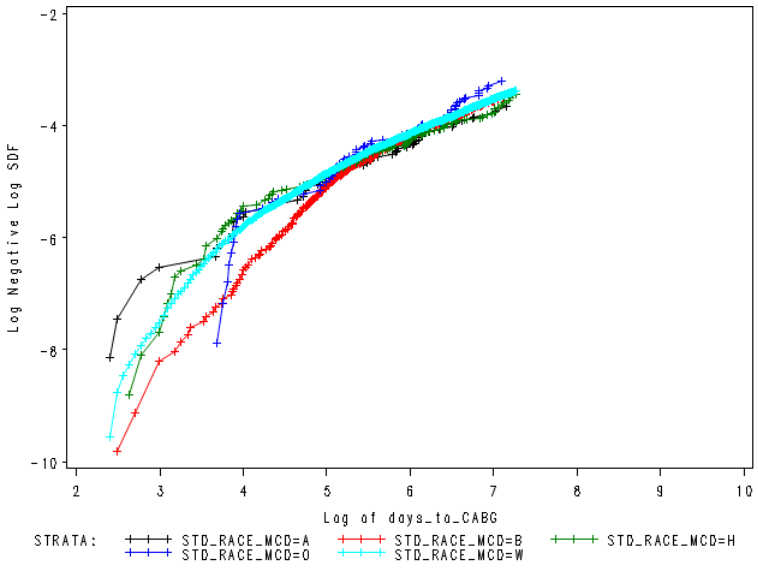
Test of proportionality (CHD outcome = AMI) across race.



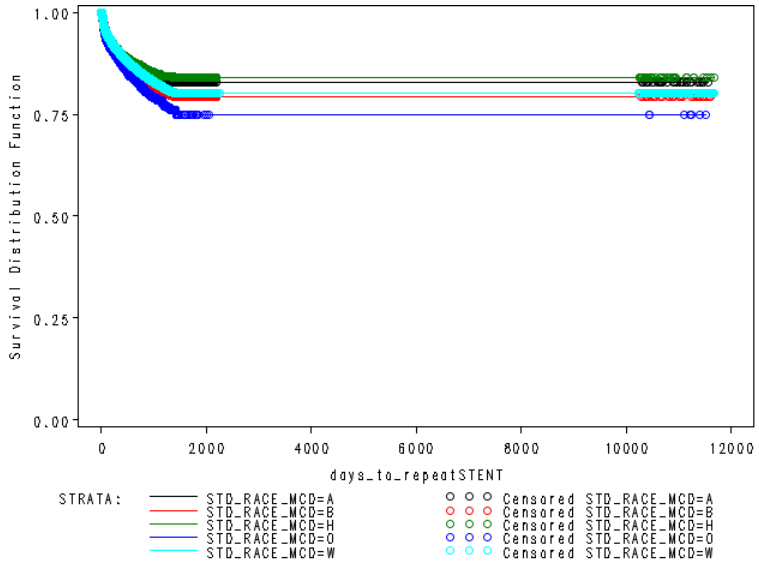


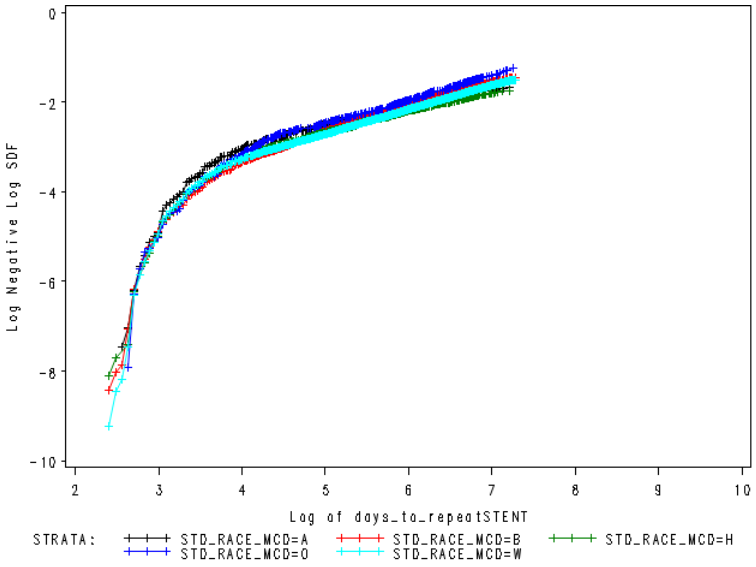
Test of proportionality (CHD outcome = CABG) across race.



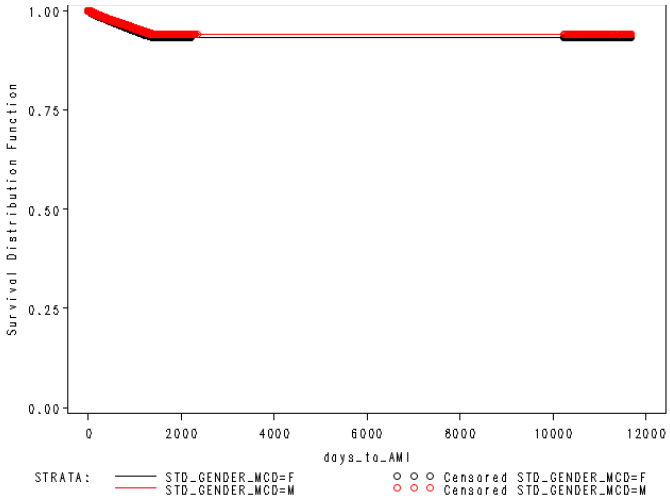


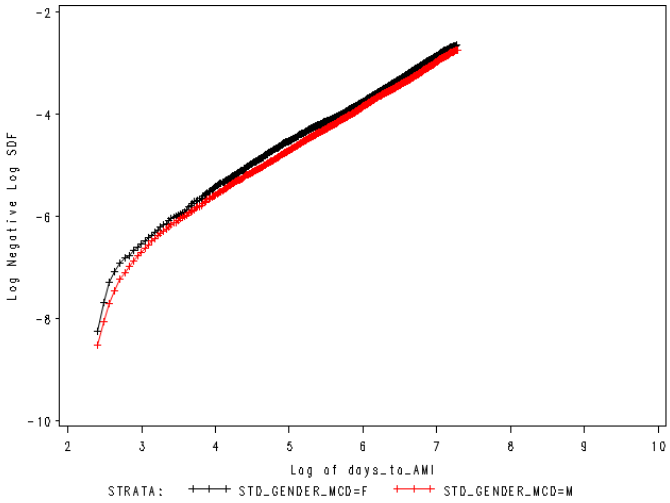
Test of proportionality (CHD outcome = repeat stent) across race.



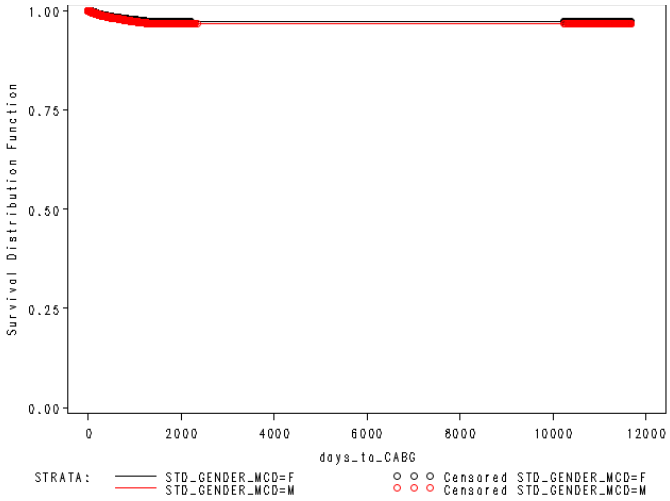


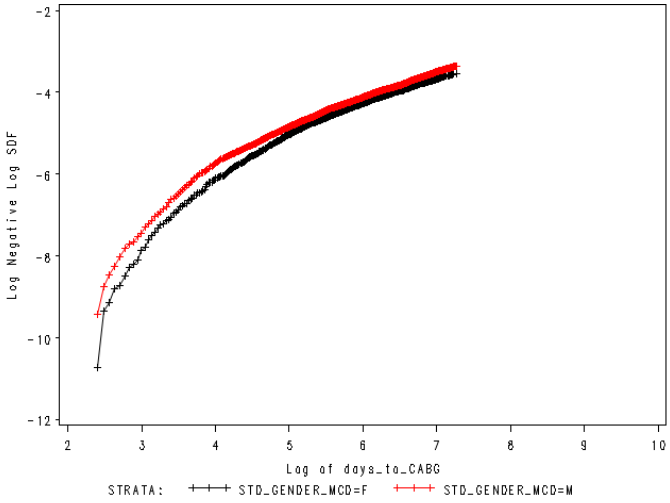
Test of proportionality (CHD outcome = AMI) across gender.



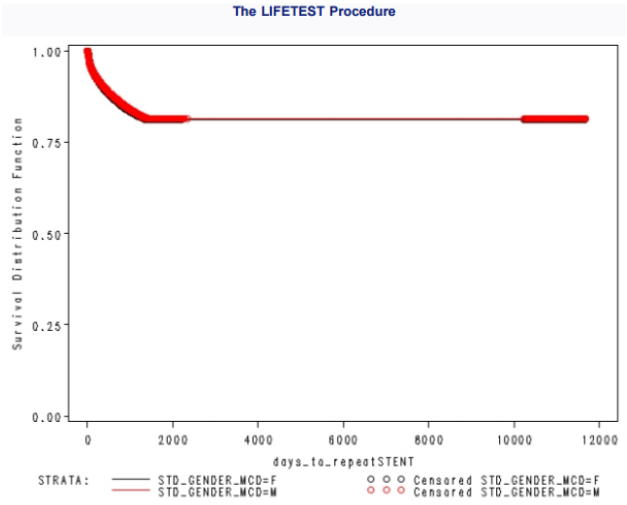


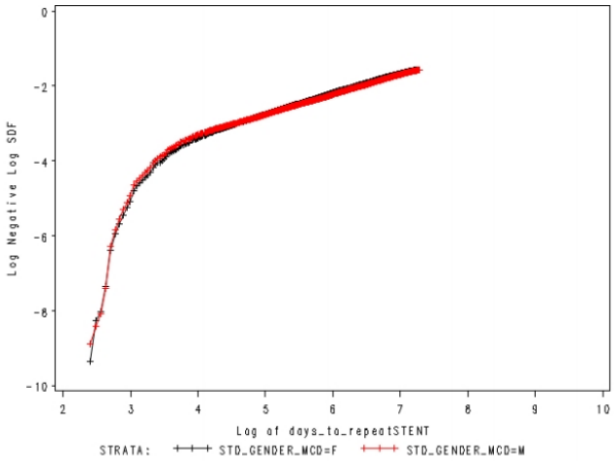
Test of proportionality (CHD outcome = CABG) across gender.





Test of proportionality (CHD outcome = repeat stent) across gender.





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